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Learning and Memory: Traditional and Systems Approaches*

Yu. I. Aleksandrov

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The aims of the present work were to consider the characteristics of learning and memory from the point of view of a systems approach and to compare this view with the traditional approach. Neuron activity is regarded not as a response to the synaptic influx resulting in excitation but as a means of altering the cell's relationship with its environment, whose "action" is to eliminate discordance between the cell's "needs" and its microenvironment. The neuronal mechanisms of learning and consolidation of memory are regarded not as formation of a stable increase in the efficiency of synaptic transmission in circuits of connected neurons, but as a system genesis event which confers new system specializations on neurons which do not have to be directly connected synaptically. The roles of the processes of selection, reconsolidatory modification of previously formed memories, gene activation, neurogenesis, and apoptosis in systems genesis occurring both in normal and pathological conditions are discussed. Individual development is regarded as a sequence of system genesis events. The systems approach is applied to the phenomenon of long-term potentiation. In conclusion, a scheme including different types and stages of memory formation is presented.

KEY WORDS: neuron, gene expression, neurogenesis, apoptosis, consolidation, reconsolidation, long-term potentiation, systems genesis, pathology.

The question of learning and memory is among the most intensely studied in neurobiology. The present article discusses the question of learning and memory from the point of view of a systems approach, which has been developed over many years in systems psychophysiology and is based on functional systems theory. The views of systems psychophysiology are original but should not be regarded as isolated from other areas of science. Assessment of the content of a whole series of theoretical and experimental reports which have appeared in recent years in authoritative scientific journals leads to the conclusion that there is a new phase in the movement of science, from "stimulus" to "target" and "holistic" determinism, to the assertion of a systems construct, and to an emphasis on individual activity. This movement is still not a major direction in the development of science, but continues to receive increasing support, to be made "official" (see, for example, [54, 94]); here and subsequently, more developed presentations of the literature can be found in the publications in the reports presented at the Second Simonov Conference and in other articles [1–4, 34, 36, 37].

Despite the tendency noted above, which continues to the present day, there are significant differences between the systems and traditional paradigms. Naturally, the approach to the experimental study of the characteristics of learning and memory and to the analysis of the resulting data depends significantly on the methodological approaches of the experimenter. Empirical manifestations are converted to facts, which are interpreted within the framework of a theory. Thus, a single manifestation can be interpreted as factually different by different authors working with different theories.

For this reason it is important not only to demonstrate how the characteristics of learning and memory are assessed from the point of view of the systems approach, but also to compare this approach with the traditional one.

V. B. Shvyrkov Laboratory for the Neurophysiological Bases of the Mind, Institute of Psychology, Russian Academy of Sciences, Moscow; e-mail: nyualex@psychol.ras.ru.

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The conceptual apparatus of this version of the systems approach has for some years been described extensively (see, for example, [1, 2, 5, 10, 30, 31]). We note here only that this is completely necessary for subsequent expounding of the logic of systems analysis of this question.

DETERMINATION OF NEURON ACTIVITY

From the Neuron as a Summator to Its Integrative Activity

Traditionally, the neuron is regarded as an element forming part of a conducting structure of greater or lesser complexity, for example in a reflex arc. In this view, the function of a neuron is to facilitate the conduction of excitation. The stimulus is the presynaptic spike and the response is the spike of the postsynaptic neuron. In other words, the neuron, like the body, responds to stimuli.

The most important event in the development of functional systems theory was the definition of the system-forming factor – the result of the system, i.e., the useful adaptive effect in relation to the body and its environment achieved by operation of the system. Thus, the behavioral determinants in the functional systems theory are not events occurring prior to behavior, i.e., stimuli, but events occurring in the future, i.e., the results [10]. However, the functional systems theory also recognizes not only the concept of a "result," but also the concept of a "trigger stimulus." This combination, as suggested by the author, is reflected in the eclectic nature of the classical version of the theory. The apparent need to use the concept of a "trigger stimulus" becomes superfluous when the behavioral act is considered not in isolation but as a component of a behavioral continuum: a series of behavioral acts performed by an individual throughout life. The next act in the continuum is performed after achievement and assessment of the result of the previous act. There is no place in the continuum for the stimulus, including the trigger stimulus [30].

The decisive step on the pathway to the formation of the systems approach for understanding neuron activity was made by Anokhin [10]. The concept of the integrative activity of neurons, assigned to them in place of the traditional "summing" concept, which regards the neuron as a summator and conductor of excitation in the reflex arc, is replaced in systems theory by the view that the generation of action potentials by neurons is a mechanism for achieving the system's result and are the consequence of intraneuronal chemical processes. However, although this new concept emphasizes the role of intercellular contacts in the *exchange of metabolic substrates* between cells, neuron activity is nonetheless regarded as a reaction occurring in response to a stimulus – the spike activity of presynaptic neurons.

The Neuron as a "Body" within the Body

The next step in the development of systems concepts of the determination of neuron activity was that of obtaining support for the view that the neuron, like any living cell, performs a genetic program requiring metabolites arriving in the cell from other cells [31]. The activity of a neuron, like the behavior of the body, is not a reaction to a stimulus, but a means of altering its relationship with its environment, whose "action" leads to achievement of a result. The *sequential nature* of events in the activity of a neuron is comparable with that characterizing the active, directed body.

In other words, the activity of a neuron, like the behavior of a body, is regarded not as a reaction but as a means of altering its relationship with its environment and directed to a future "action" which eliminates discord between the "needs" and the microenvironment, particularly that due to changes in the synaptic influx. Such a change, if it leads to satisfaction of the ongoing metabolic "needs" of the neuron, i.e., to the achievement of its metabolic "result," leads to termination of spike activity.

It has been suggested that discordance between the "needs," which are genetically determined, and the actual incoming metabolites, can occur both as a result of genetically determined changes in the metabolism of the cell and as a result of changes in the influx of metabolites from other cells.

Thus, within the framework of these concepts, the neuron is not an "encoding element," "conductor," or "summator," but a body within the body, with its own "needs" generated by metabolites arriving from other elements.

The role of most chemical compounds arriving in the cell's "microenvironment" is to change the properties and rates of synthesis of intracellular proteins or to induce the synthesis of new proteins. The metabolism of a neuron is also influenced by neurotransmitters released from the terminals of neurons making contact with it. Binding to "its" receptors, the transmitter not only changes the permeability of ion channels, but also affects intracellular processes which induce intracellular metabolic transformations (see, for example, [29]). However, changes in ion channel permeability also have significant influences on cell metabolism, i.e., transmembrane transport of metabolites and maintenance of intracellular pH [86].

Achievement of a Result at the Level of the Whole Body and the Individual Cell

Along with the similarity [66], the characteristics of the maintenance of the viabilities of neurons and unicellular organisms have a number of significant differences. The unicellular organism (and also the multicellular) can fulfill its metabolic needs exclusively by means of its own activity. The neuron supports its metabolic "needs" by combining with other body elements to form a functional system. Their interaction and cooperative activity lead to the achievement of the result and a new relationship between the whole individual and its environment.

"Externally," at the level of the whole individual, analysis of observed behavior shows that the result is described as a defined relationship between the body and its environ-

ment which terminates the action directed to achieving this result, making the following act possible. "Internally," at the level of individual neurons, achievement of the result is the satisfaction of the metabolic "needs" of neurons and terminates their spike activity. *This activity is the neuronal basis of behavior.* Figure 1 illustrates the cessation of neuron activation in the cingulate and anterolateral areas of the rabbit cortex on achievement of operant behavior: seizing of a ring or contact with a pedal [41].

The "Action" of a Neuron

The "action" of a neuron, its spike activity, not only affects the microenvironment, but also alters the discharging neuron itself; its sensitivity to the synaptic influx is significantly modified [45]. This modification can be regarded as a measure of the readiness of the neuron for future influx associated with its activity. In other words, the discharging of the neuron not only provides its required metabolic influx but also prepares it to "utilize" this metabolic influx [2].

Considerations within the framework of the traditional approach to understanding the neurons as a conductor of excitation often raise the question formulated by Kandel: "Why are there different neurotransmitters if only one is sufficient to mediate the transmission of all electrical signals?" (see [23]). A variety of theoretical constructs aimed at answering this simple question have been presented ([23] and other articles in *Zh. Évolyuts. Biokhim. Fiziol.*, Vol. 26, No. 5 (1990)).

From the point of view of the systems determination of neuron activity, the neurotransmitter is no longer regarded as the stimulus acting on the neuron (or an individual locus on the neuron) – the neuron is not regarded as a transmitter of electrical signals. Instead, neurotransmitters or mediators (biologically active substances operating as messengers in the process of transmitting excitation by means of synaptic influences) are regarded as *metabolites* – substances needed for cell metabolism and contributing to satisfaction of the cell's "needs." Given the variety of these needs, there is no surprise that there is a variety of mediators. The question of the "multiplicity of neurotransmitters" thus becomes a question of identifying the specific features of metabolic patterns associated with satisfying one or another "need."

LEARNING AS THE FORMATION OF "TRACES" AND AS A PROCESS OF SYSTEM FORMATION

The Systems-Selection Concept of Learning

It is now widely accepted that many features of the modification of the functional and morphological properties of neurons, as well as the regulation of gene expression underlying learning in adults are similar to those defining the process of maturation, which characterizes the early stages of ontogenesis [6, 7]. This provided the authors with grounds for regarding learning as a reactivation of the maturation processes which occurred in early ontogenesis. In functional systems theory, the concept that system formation does not occur only in early ontogenesis [10], but also in adults, has long been accepted. The formation of a new behavioral act in an individual at any age is a system genesis event – the formation of a new system.

Subsequent studies led to the conclusion that consideration of the history of formation of behavior, i.e., the history of sequential system genesis events, is fundamental for understanding differences in the roles of individual neurons in supporting behavior [1, 6]. The systems selection concept of learning was subsequently developed [31], which is in accord with Edelman's concepts of the selective (selection from a multiplicity of brain neurons with defined properties) rather than the instructive (changes in properties, "instruction" of cells by the corresponding signals) principle underlying the formation of neuronal combinations at the early and late stages of ontogenesis [52].

According to Edelman, selection occurs as early as brain maturation in early ontogenesis, during which many neurons die. The selected cells constitute the *primary assortment*. The *secondary assortment* is formed as a result of selection occurring on learning during behavioral interactions with the environment.

From the systems point of view, the formation of a new system is regarded as the formation of a new element of individual experience during the process of learning. The formation of new functional systems during learning is based on the selection of neurons from a "reserve" (presumptively low-activity or "silent" cells). These neurons can be compared with the primary assortment and are designated *prespecialized* cells. During the learning process, a selection is made from these cells of those which *become specialized* in relation to the to the system corresponding to the newly formed behavioral act. Neuron selection depends on the characteristics of their metabolic "needs." These neurons can be compared with the secondary assortment defined by Edelman. Specialized neurons in relatively newly formed systems – systems specialization – are permanent. Thus, the new system is an "addition" to previously formed systems and is "layered" upon them.

The fact that learning involves new neurons rather than "retraining" of previously "trained" neurons is in agreement with data obtained by several groups [44, 92, 95, and others] showing that the brains of various animal species contain large numbers of "silent" cells, that there are increases in the numbers of active cells on learning, and that the newly formed neuron specializations are permanent (in experimental terms, throughout the long-term observation period, i.e., weeks or months).

Extraction of Material from Memory During the Performance of Behavior

How is material in memories formed during learning used in the performance of behavior? Behavior has been

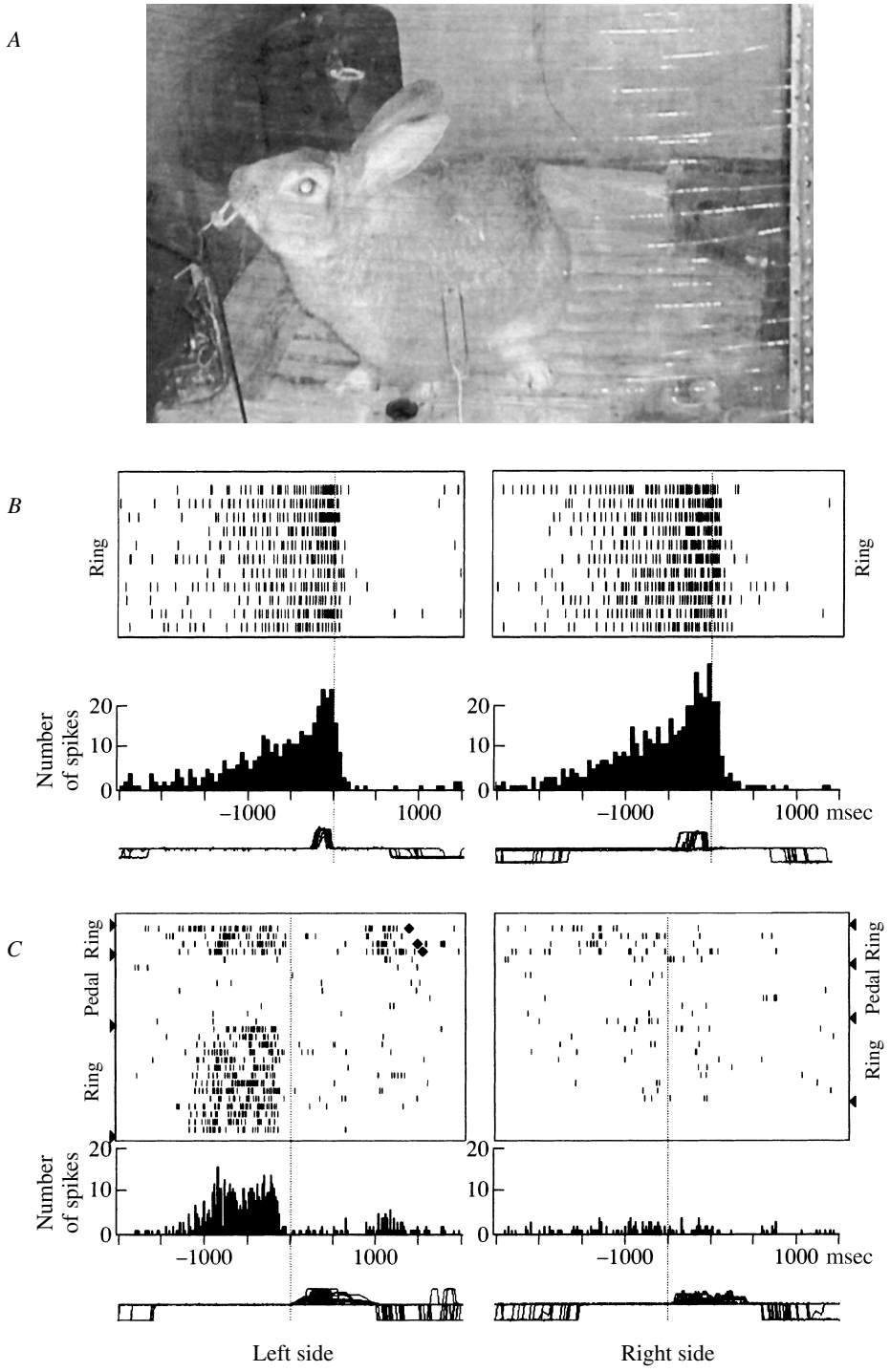

Fig. 1.

Fig. 1. Activation of neurons in the rabbit cingulate and anterolateral motor cortex ceases on achievement of the results of operant learning. The experimental cage (*A*, *D*) in which operant food-procuring behavior is performed by the animal pulling obliquely on a ring (*A*) or pressing a pedal (*D*) is fitted with paired feeders automatically delivering reward on pressing the corresponding pedal (located on the same wall of the cage as the feeder) or pulling the corresponding ring. Beneath are shown raster plots of spike activity and histograms of neuron activity in the anterolateral (*B*, *E*) and cingulate (*C*, *F*) areas of the cortex. *B*) A neuron in the anterolateral cortex is activated on approach to and seizing and pulling of the ring. *E*) A neuron in the anterolateral cortex is activated on contact with the right but not the left pedal. There is no activation on approach to and seizing of the ring. *C*) A neuron in the cingulate cortex is activated on seizing of the left but not the right ring. There is no activation on approach to or pressing of the pedals. *F*) A neuron in the cingulate cortex is activated both on approach to and seizing and pulling of the left ring and on approach to and pressing of the left pedal. In *C* and *E*, raster plots

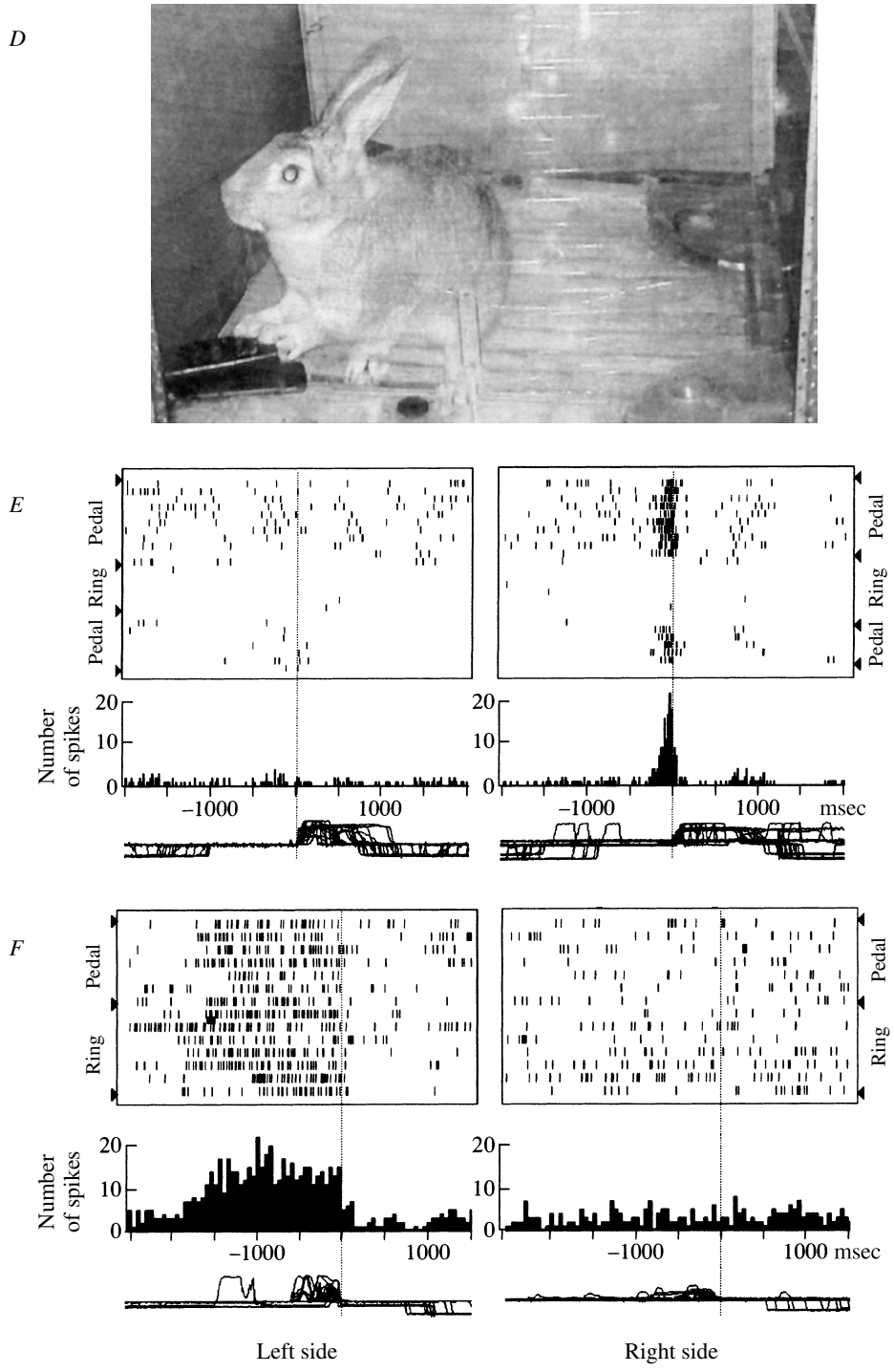

Fig. 1. Continued.

and histograms are constructed in relation to the start of pulling the ring and the start of pressing the pedal respectively; in *B* and *F*, plots are relative to completion of pulling the ring and pressing the pedal. The vertical lines passing through all components in fragments *B–F* identify the time point at which raster plots and histograms were constructed. Vertical bars on raster plots show individual neuron spikes and horizontal bars show sequences of spikes in an individual cycle of the food-procuring behavior. Cumulative histograms with a channel width of 20 msec (for C and *E*) and 50 msec (for *B*, *F*) are shown beneath the raster plots. The lowest plots are behavior actograms for all cycles of the food-procuring behavior performed by the animals during recording of spike activity from the corresponding neuron. Upward displacement of lines on the actograms show pulling of the ring or pressing of the pedal; downward displacements show lowering of the animal's snout to the feeder. In *C*, diamonds show repeat pulls; in *F*, rectangles show the first pull when the animal performed the operant act several times in the food-producing cycle.

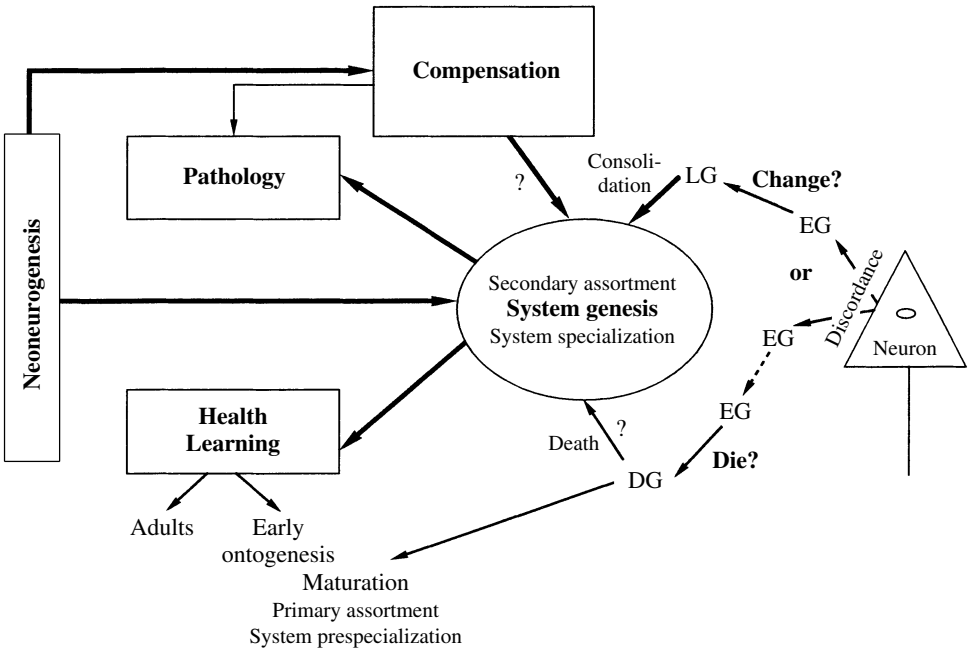

Fig. 2. Change or die? Theoretical scheme. EG = "early" genes; LG = "late" genes; DG = "death" genes. For explanation see text.

shown to be mediated not only by the execution of new systems formed on learning the acts making up this behavior, but also by means of simultaneous execution of older systems formed at earlier stages of individual development. These latter can be involved in supporting a multitude of behaviors, i.e., those associated with systems which are common to different acts.

Thus, the systems structure of behavior reflects the history of its formation. In other words, performance of behavior is execution of the history of the formation of the behavior concerned, i.e., a multitude of systems, each of which fixes a stage in the establishment of a given behavior during individual development. It follows logically that the neuronal support of *externally identical* behaviors can differ if the histories of the formation of these behaviors differ; this has received experimental support [5].

Given that the history of the formation of a behavior underlies the features of its execution, it is clear that "historical nihilism" has negative impact on our understanding of experimental data. The effects of the characteristics of individual development on brain activity are seen not only in studies of the neuronal bases of behavior, but also in the solution of a wide variety of investigative tasks [53, 57, and many others].

Neoneurogenesis

Clear evidence has now been obtained for the occurrence of neoneurogenesis in adult birds, as well as in mammals, including humans [46, 56, 79, 82]. The number of surviving neurons reappearing during neurogenesis in adult animals has been shown to increase when animals are kept in enriched environments and specialize in relation to the new systems.

Neoneurogenesis can also be important for the enrichment of sets of neurons of the primary and/or secondary assortments in pathological conditions [98] (Fig. 2). It may be that enrichment compensating for neuron death, including that of specialized cells, can also occur in health (see below for neuron death in health). The very hypothetical nature of this suggestion is emphasized by the question mark in Fig. 2 (arrow from the Compensation fragment). At the same time, considering that prespecialized cells (the primary assortment) are a reserve for the formation of new memories, this suggestion is in good agreement with the view that intensification of cell proliferation in a *given* element of learning is important for *future* learning [82].

As regards the compensation for specialized cells (the secondary assortment), it is difficult to say that this could occur outside the framework of a systems process, requiring activation of cells linked to the system and trials directed achieving its result. It may be that such trial concordances between new and "old" cells develop during reconsolidation processes (see below).

Memory Consolidation: Formation and Fixation of "Traces" via Increases in Synapse Efficiency

The question of the formation and consolidation of memory has been addressed using the most state-of-the-art methods and is based on current conceptual schemes, though most of these schemes and investigations are based

on Descartes' concept formulated *more than 300 years ago*: *"traces exist because of pores in the brain through which the spirit has previously passed become more permeable when the spirit passes through them again. And the spirit can pass through these pores more easily.*

In accordance with this idea, it is important to understand the mechanisms for increases in pore permeability, which brain structures have more such pores, whether all pores have the property of variability, how long increases in pore permeability last, etc. Thus, all the various approaches to understanding consolidation take long-term increases in synaptic conduction in a reflex arc (arcs), networks, etc, as the most basic of its features.

From the systems point of view, the neuron is not regarded as a conductor of excitation. Therefore, the question of the mechanisms of increases in the efficiency of conduction does not arise.

Which features can be identified in the processes of the formation and retention of memories when addressed from the systems point of view? And if the mechanisms of increases in synaptic conductivity in circuits of connected neurons are not regarded as the basis of these processes, how do we deal with changes in excitability and morphological rearrangements of neurons in learning in the face of the enormous amount of material obtained from studies of such mechanisms, particularly the many reports demonstrating activation of the cell's genetic apparatus? The answer to the first question requires a number of prior comments on reconsolidation.

Reconsolidation in Memory Reactivation and Learning

Bartlett [43] suggested that the view that "reproduction from memory" should be regarded as the "repeated excitation of unchanged 'traces'" should be completely discarded (see also [13]). The molecular-biological characteristics of reconsolidation of memory and underlying modification occurring after repeated actualization have now been identified (see, for example, [87]). Activation of a memory, like its formation, requires protein synthesis for reconsolidation processes. Thus, protein-dependent consolidation processes can be linked not only with "new" memories, but, more generally, with "active" memories [76].

The concept of reconsolidation modifications does not contradict the position presented above regarding the permanence of the systems specialization of neurons. Reconsolidation does not alter the modifications leading to the formation of long-term memory [75]. Bezdenezhnykh demonstrated that even after major rearrangements of the neuron microenvironment by microiontophoretic application of high neurotransmitters concentrations, which significantly alter the nature of spike activity (frequency, duration of activation, etc.), the neuron continues to be involved in supporting behavioral acts relevant to the system to which it is specialized [11]. The author suggested that the permanence of specialization is based on "system metabolism," which controls homeostatic processes directing to maintaining the involvement of the neuron in the system.

Behavioral data obtained in Pavlov's laboratory [20] led him to the conclusion that the addition of new conditioned reflexes immediately echoes the state of the previous reflexes. We regard learning as a specialization of a new group of neurons relevant to the newly formed system and "addition" of this to the previously formed systems. It is logical to suggest that this addition requires mutual accord between the new element and the previously formed elements and leads to reconsolidation modifications of these latter elements.

We have previously presented data providing evidence supporting the view that neurons belonging to a given system and involved in supporting a single behavior do not change their system specialization but rearrange their activity when this system becomes involved in supporting another behavior [1]. Data obtained in experiments based on defining system specializations of neurons by sequential formation of different behavioral acts have recently led to the conclusion that a previously formed system for a behavioral act changes after learning a new act. The reconsolidation modification undergone by the previously formed, "old," system on appearance of a related new system was termed *"accommodation"* reconsolidation [37].

Consolidation from the Systems Point of View

From the systems point of view, the formation of a new memory is regarded not as forming a path and generating "traces" due to increases in the efficiency of synaptic connections between the neurons involved. Formation of a new memory is taken as the formation of a new system of simultaneously activated cells within the body, including neurons located in very diverse brain structures and not obligatorily connected by direct influences.

This position arises from the theoretical underpinnings of the systems approach. However, experiment data lead to similar conclusions as authors coming from different theoretical positions. Horn notes that cross-correlation analysis of chick forebrain neuron activity does not support the view that learning involves strengthening of connections between neurons, as would be expected on the basis of the formation of "Hebbian" ensembles. "It is more likely," he concludes, "that neurons form a parallel [organized] set, with no significant direct connections, which supports a greater efficiency of storage [in memory] than a system of directly connected elements" [61, p. 121].

I suggest that this position leads to a contradiction with the traditional view of consolidation processes. And despite the need for well-grounded views, we cannot be dogmatic in considering these processes [75, p. 467]. Horn's position, *within the traditional approach*, can nonetheless be regarded as entirely original.

It follows from the above comments that analysis of the formation of memory requires consideration not only

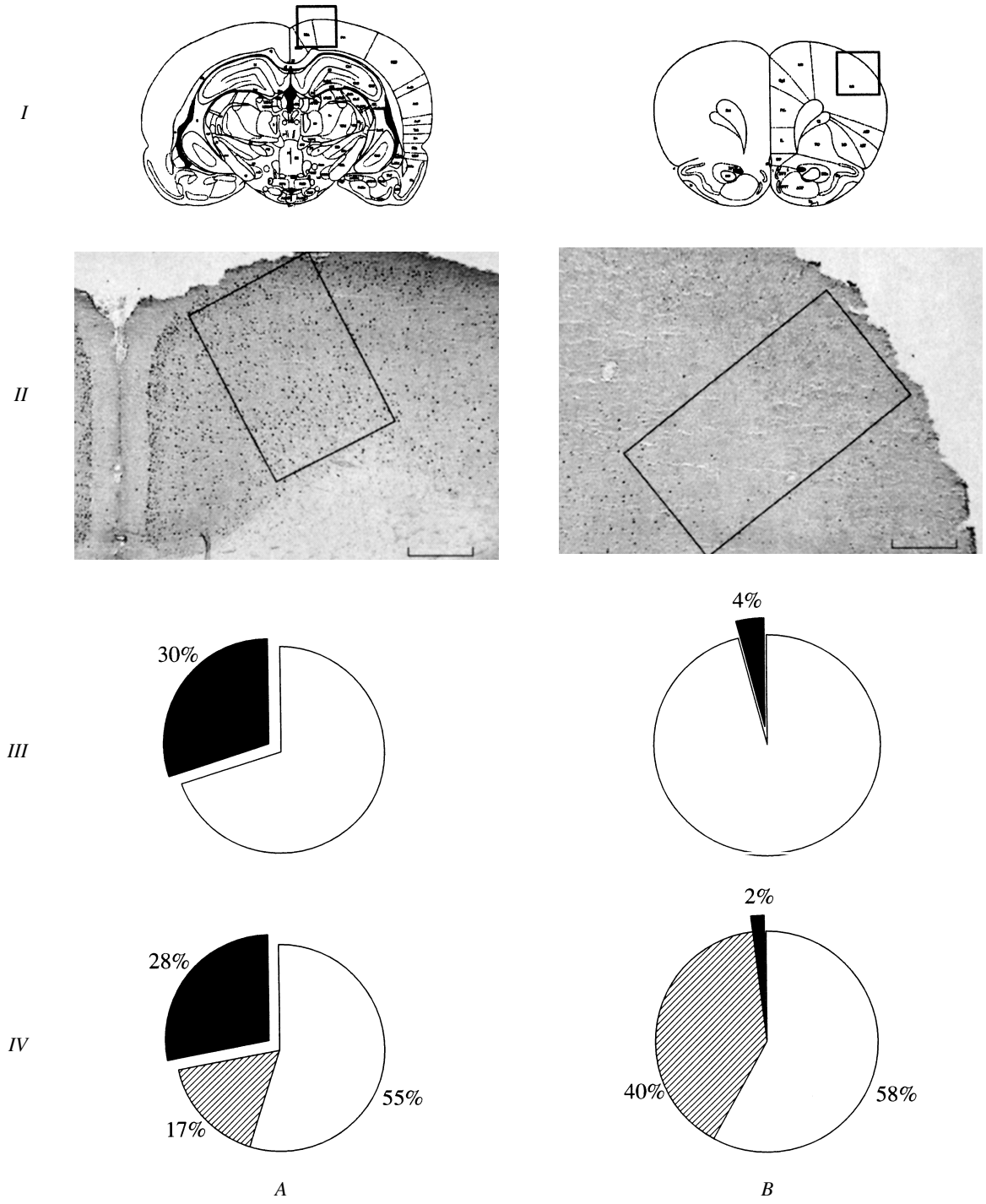

Fig. 3. Comparison of the relative numbers of Fos-positive cells (*III*) with the patterns of behavioral specialization of neurons (*IV*) in the cingulate (*A*) and anterolateral (*B*) cortex. *I*) Diagram showing frontal sections identifying the study areas. *II*) Microphotograph of frontal sections showing Fos-stained neuron nuclei in rats which formed a new behavior. Calibration: 500 μm. *III*) The dark sector shows the proportion of neurons expressing c-Fos (%); the light sector shows cells not expressing c-Fos. *IV*) The dark sector shows the proportion of neurons associated with "new" systems formed on training rats to an operant act consisting of pressing a pedal in a food-procuring behavior; the shaded sector shows the proportion of neurons associated with "old" systems formed at stages of individual experience preceding training to the operant food-procuring behavior; the light sector shows the proportion of neurons lacking constant activation in this behavior. This shows that the cingulate cortex contains significantly more cells expressing c-Fos and cells specialized for the newly formed system of the operant behavioral act than the anterolateral cortex.

of the appearance of its new material, but also modification of previously formed material. The systems description of the consolidation process includes two groups of inseparably linked processes.

1. The process of *system specialization*: morphological and functional modification of neurons associated with their involvement in supporting the newly formed system.

2. The processes of *accommodation reconsolidation* are due to the recruitment of existing systems into the ongoing structure of individual experience: morphological and functional modification of neurons (without alteration of their system specialization) belonging to previously formed systems.

The literature contains well-grounded views whereby rearrangements of memory can occur because as a result of "routine" reorganization (rearrangement of the relationships between components of existing memories) and as a result of a "heuristic" act forming a new component and modifying existing memories [21, 81]. The processes of system specialization and accommodation *reconsolidation* listed above describe the second type of rearrangement. As regards the first, the processes of morphological and functional modification of neurons seen during learning without formation of a new system can be termed "reorganization" reconsolidation. It is likely that one measure of this type of learning is provided by the slow increase in the effectiveness of behavior rather than the sharp transition from a trial period to a period of effective behavior which occurs, for example, on training to operant food-procuring behavioral acts when, as known, new elements of experience are formed in relation to learning these acts [1–6, 31].

This slow improvement in behavior can be demonstrated using examples (not evidence) from simulation experiments and animal experiments. In simulations of an agent based on the Actor/Critic algorithm, the number of trials needed for learning seeking and food-procuring behavior is of the order of thousands. In this model, learning of the new behavior occurs as a result of the influences of new sensory situations on memory components already in the agent's possession, without formation of new components [17]. In Gorkin's experiments, rats learned to discriminate similar and differing pairs of sounds. The dynamics of learning the task in terms of short-term memory were characterized by a very smooth and slow improvement in task execution by the animals. The animals demonstrated a tendency to solve the task not by comparing the sounds, but by simpler methods, i.e., methods not requiring a comparison procedure, for example, executing a verification action after any pair of sounds or even after the first presentation of a sound. Finally, analysis at the behavioral level is preliminary and its results do not exclude the possibility of alternative explanations.

It follows from the above that comparison of the "usual" reconsolidation, i.e., reactivation, with accommodation and reorganization reconsolidation is needed. Thus, along with the differences, a certain similarity between reactivation and accommodation reconsolidation can be identified in cases in which elements of experience take place between two extractions of the "same" material from memory in conditions in which accommodation reconsolidation did not affect the material during the process of forming the new elements. A very strong similarity can also be suggested between reactivation and reorganization reconsolidation, though the scale of rearrangements in this case is probably different. This similarity, arising in both cases because no new elements of experience are formed, appears to be reflected both in objective and subjective measures: in both cases the individual's own behavior before and after reconsolidation changes can appear the "same."

It is important to emphasize the *need for differentiation of the processes of system specialization and reconsolidation*. Learning-associated neuron modifications seen in neurophysiological, morphological, molecular-biological and other studies may be associated with both the former and latter groups of processes. Thus, for example, the appearance of activation in response to a conditioned signal has repeatedly been described in relation to those neurons which, before the combination of the conditioned and unconditioned signals, responded only to the unconditioned signal; this is primarily associated with reconsolidation rather than systems specialization (see also [1]). The same applies to learning-associated modifications of neuronal and genetic activity in the primary motor cortex [47], where the vast majority of neurons belong to "old" systems formed at the early stages of individual development [5]. The differential approach to modifications of the first and second groups is a significant step forward on the pathway to understanding the characteristics of memory formation.

The Beginning of Memory Formation – Discordance

It is accepted that the basis of consolidation is provided by morphological changes in neurons ([42]; see, however, a different point of view expressed in [40]). The initial step in the cascade of molecular-biological processes resulting in morphological modifications of neurons both in morphogenesis (early ontogenesis) and in memory consolidation in rats is the expression of "early" genes, this being a transient process which is followed by a second wave of expression, i.e., of "late" genes, which have direct relationships with the morphological modifications of neurons. The link between the expression of "early" genes and learning processes, which is long known (see [6, 7]) continues to become increasingly evident [61].

The points of view developed here led to the view that the expression of "early" genes and the formation of specialized connections are linked. In fact, data have been obtained supporting the view that the expression of "early" genes is based on the formation of neuron specialization. Gene expression is more marked in those brain structures in

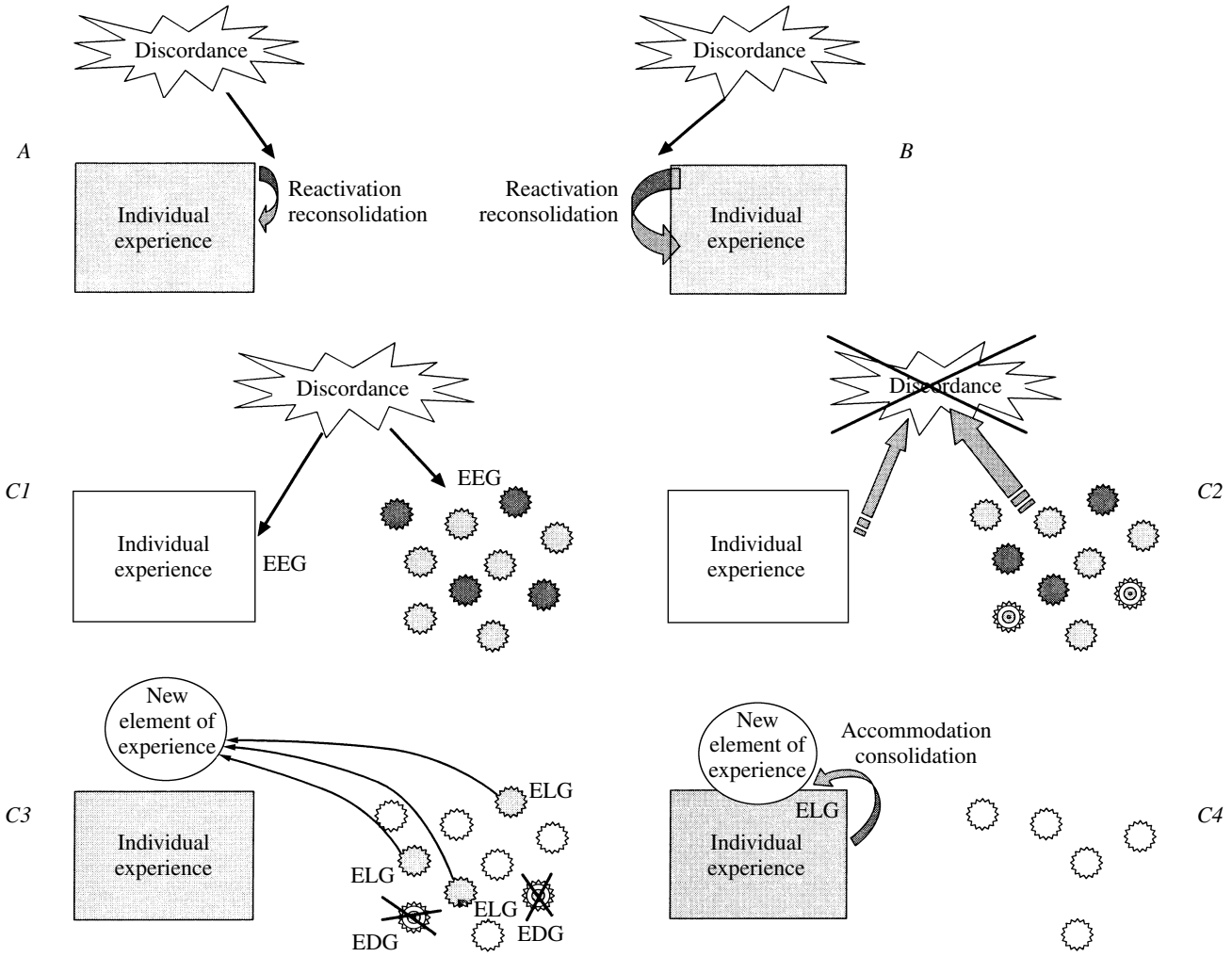

Fig. 4. Variants and modification of the structure of individual experience. *A*) Reactivation of memory in definitive behavior. Performance of behavior is a means of eliminating the discordance between the metabolic "needs" of cells and the metabolic influx to them. Discordance is eliminated by performance of a definitive behavior supported by the combined activity of cells combined into a previously formed system. Reactivation of a memory may be associated with modification of the structure of individual experience due to reactivation reconsolidation. *B*) Modification of the structure of individual experience in a new situation, limited by reorganization of previously formed relationships between systems, which are elements of individual experience. A new element of experience does not form. *C*) Discordance which cannot be eliminated by execution of existing memory (*A*) or reorganization of intersystem relationships (*B*) is eliminated by the formation of a new system, i.e., a new element of individual experience. *C1*) Expression of "early "genes (EEG) at the first stages of formation may affect both prespecialized cells (shown as circles on this and other components of this Figure) and some cells which had previously formed their specializations, i.e., belonging to systems of already existing individual experience (the set of these systems is indicated by triangles). The electrophysiological manifestation of these processes is an increase in the sensitivity of synapses to the influx. *C2*) Selection occurs during the trials process: a corresponding set (dark circles) is selected from a multitude of activated prespecialized cells, including those appearing as a result of neoneurogenesis. This is the set whose coactivation with previously specialized cells, including cells corresponding to investigative behavior, leads to achievement of the required behavioral result. At the cellular level, achievement of this result is apparent as satisfaction of the metabolic "needs" of cells and elimination of discordance. *C3*) As selection proceeds, the neuron can choose one of two pathways for involvement in systems genesis processes: it can change, by being involved in a new system, and then undergo consolidation (expression of "late" genes – ELG), or it can die. Elimination of cells (crossed-out circles; expression of "death genes" – EDG) can be regarded as "altruistic suicide" performed to overcome newly arising metabolic contradictions between cells which cannot be eliminated by any other means and which ensures the survival of other cells belonging to the same clone. *C4*) Accommodation modification of cells specialized in relation to previously formed systems (triangle) is due to the recruitment of the newly formed system into the existing structure of an individual's individual experience.

which training is followed by the detection of significantly larger waves of newly specialized neurons (Fig. 3; [25]).

Activation of "early" genes in adults can occur not only on learning, but also in hunger, stress, intoxication, nervous system lesions, and brain ischemia (see [24]). It has also been demonstrated that changes in the neuron microenvironment induce activity in previously silent cells [32] and the expression of early genes [91]. Therefore, bearing in

mind the comments above on the determination of neuron activity by discordance between the neuron's "needs" and the influx of metabolites, as well as the fact that early gene expression can be regarded as a specific manifestation of cell activity [48] arising in novelty situations [9], it is logical to suggest that *discordance* is common to all the situations noted above, including learning. This arises because previously formed means of according the metabolic "needs" of neurons *in the framework of the existing structures of experience* are ineffective in conditions of stable changes in the neuron microenvironment. We note that discordance is, so to speak, an interparadigm concept used not only in functional systems theory but also in other conceptual schemes, for example, reflex theory [26].

The search for new means to eliminate discordance includes both modification at the level of behavioral adaptations, but also molecular-genetic and morphological rearrangements. These modifications occur both in *health* and in *pathology*.

In "folk science," health and pathology are seen as fundamentally different states. In objective science, it has long been accepted that processes termed pathological are not disorganized or chaotic, but only different – adaptations to ongoing conditions, acquired during the process of evolution. There is no pathological process which does not have a prototype in health. The health–pathology disjunction is not real; there is a continuum of states from the so-called "normal" to the "pathological" [12, 16, 58, 74, and others]. Adaptive changes arising in conditions of pathology can, as in health, be regarded as systems processes affecting the whole body and directed to achieving positive results and including rearrangements occurring on formation of long-term memory in health [8, 36, 37, 58, 78, and many others].

Given the similarity just noted, as well as consideration of the similarity in the molecular-biological processes underlying maturation and learning, it is not surprising that rejuvenation (reactivation in the adult of mechanisms of mechanisms activated in early ontogenesis) occurs not only in learning, but also in pathology [49]. The purposes of the following discussion require emphasis to be placed on the fact that the mechanisms reactivated in pathological conditions in adults include apoptotic cell death [99].

The neuron, as noted above, can support the "needs" of its metabolism by joining with other body elements to form a functional system extracted from memory. Achievement of a result by this system eliminates the discordance between the "needs" and the state of the neuron microenvironment. These dynamics characterize the situation of definitive behavior.

The learning situation in health and recovery from pathology (for example, after strokes, traumatic brain injuries) is specific in that the problem of resolving the "needs" cannot be solved using any means of accordance available to the individual (i.e., within the framework of experience that the individual has already had). In this situation, *discordance* differs from that occurring in definitive behavior: it is *eliminated* by the search for and fixation in memory of new versions of element combinations and the *execution of system genesis processes* (Fig. 2; see also Fig. 4).

Thus, the content of this section can be summarized in terms of Socrates' assertion with replacement of only the word "surprise:" *discord is the source of all wisdom. From discordance through concordance to consolidation.*

When systems genesis processes occur successfully, new systems are formed which, when executed, ensure accord and satisfaction of the metabolic "needs" of neurons.

How is the search for a means of obtaining concordance of cell metabolism during the learning process on analysis of "external" behavior or brain electrical activity to be detected? At the behavioral level, orientation-investigative behavior can, as noted, usually be used, this ending with achievement of a desired result. This is followed by the relative stabilization of behavioral measures.

Overall brain activity in humans changes not only during the process of learning a skill, but also hours (and days) after behavioral criteria indicate that the subject has learned (see [64]). Animal experiments also demonstrate that both the characteristics of neuron activation and the number of activated cells change over a period of hours and days after the first performance of a behavior (see [55, 61, 62, 84, and many more]).

Data obtained by Svarnik et al. [24] show that the number of brain cells showing early gene expression is many times larger than the number of neurons in the area in which specialization of the system corresponding to the formed behavior is observed. We suggest that some of this multitude of genetically activated cells are neurons specialized with respect to systems corresponding to previously formed acts and that expression within these cells reflects the onset of the process of accommodation reconsolidation. Most of these cells are prespecialized cells and their genetic activation is a prerequisite for transfer of these cells to the state of readiness for selection during the process of performing trials. It is during the performance of trials that those cells which subsequently enter the class of cells specialized with respect to the formed system are selected from the whole set of activated (genetically and, probably, in terms of spike activity).

The occurrence of this selection and changes occurring in the neurons supporting the formed behavior is provided by the increase in the number of neurons activated in 100% of cases (i.e., in every performance of the act specific for that cell) as memory consolidates, as observed in experiments reported by Kuzina et al. [19]. Decreases in the variation of activity would appear to be associated with the completion of selection and stabilization of the set of neurons involved in the newly formed behavior.

Some cells have been shown to be activated only at the initial stages of learning, with cessation of activity, without reappearance, after the behavior has stabilized [88, 97].

Some of these cells probably belong to the class of prespecialized neurons activated during trials. The following may apply to the rest of these cells.

Various areas of the brain (hippocampus, entorhinal, prefrontal, and cingulate areas of the cortex, amygdala, etc.) contain neurons whose activity is specifically associated with the situation of *novelty* [83, 84]. The first trial acts may be performed by means of coactivation of a transient population of previously specialized and prespecialized neurons, as well as cells which are currently termed "novelty" neurons. Coactivation facilitates both completion of the trials and *achievement of the first positive results during learning*. After stabilization of the behavior, "novelty" neurons terminate their activity. This indicates extensive reorganization of executed memory material and, perhaps, initiates a further, additional, wave of selection.

Within the framework of the traditional approach, the role of these neurons is said to be to support attention, to increase the level of consciousness, etc., and thus to act on the neural networks undergoing the learning process. The systems description requires identification of systems directed to achieving a defined result, of which "novelty" neurons are members.

Simonov commented that "definitive evidence" has been obtained for the existence in animals of investigative behavior creating "a separate need" to contact objects, though the "practical value" of this was unclear. When an individual finds itself in an unfamiliar situation, the primary task is to classify the situation as one in which "approximation" behavior is appropriate or one requiring "avoidance" (see [34]). The achievement of this "classification" result allows progress to a behavior directed to achieving the next result in the behavioral continuum. What this next result will be is determined by the individual's motivation and the result of the investigative behavior, i.e., the elements of the memory domain (or subdomain) can be executed.

"Altruistic suicide"

Thus, "early" genes are expressed when the organism lacks experience of satisfying the metabolic "needs" of cells in a given situation, when repeated spike activity from coactivated neurons does not lead to achievement of a result. This expression can be regarded not only as the beginning of a cascade of processes leading to consolidation, but also as a prerequisite for activation of other transcriptional components – the basis of the cell's "decision to live or die" [68, p. 2736]. If the discordance between the "needs" of neurons and their microenvironment is *protracted*, neurons are hyperactive and one wave of "early" gene expression follows another. In these cases, neurons can express "death" genes whose activation leads to nerve cell death (Fig. 2). Thus, when discordance between the "needs" of a neuron and its microenvironment cannot be resolved within the framework of existing experience, the cell has the following alternatives in both normal conditions (early ontogenesis and adults) and in pathology: it can change by taking part in a systems genesis (formation of a new system, consolidation) or die (Fig. 2) (for a more detailed discussion see [3]). The involvement can be in the form of a system specialization or accommodation or reorganization reconsolidation (see above).

Within the framework of these concepts, the many repeated waves of "early" gene expression at the initial states of ontogenesis may be associated with both intensive morphogenesis and the formation of all new behavioral acts as well as with death of many nerve cells during this period [77] (see Fig. 2).

Cell death is often seen during maturation in early ontogenesis and in pathological conditions, when the individual's existing experience is inadequate to produce accord of the metabolism of the body's cells. Data have been obtained which provide evidence supporting the occurrence of apoptosis in the brains of healthy adult individuals. It has been suggested that apoptosis is needed for the functioning of the body as a whole in animals [63, 69, and others] and plants [22]. These data, considering the concept that systems-genetic characteristics are a common principle underlying the realization of the processes of a) maturation, b) learning at any stage of ontogenesis, and c) adaptation to and recovery from pathology, suggest that the "change or die" choice exists in normal conditions. Elimination of neurons as an outcome of neuroselection in early ontogenesis, whose importance in forming the behavioral repertoire elicits no doubt, also makes a contribution to systems genesis in adults (Fig. 2; question mark in diagram by the arrow labeled "death" indicates the hypothetical nature of neuron death as a factor in systems genesis).

This position does not lead to the choice between systems genesis and death, but to two interrelated pathways of systems genesis: modification of the neuron or death of the neuron. The link between these two pathways occurs not only at the stage of "early" gene activation, but also at the stage of activation of caspase-3, which is involved in the cascades of both apoptotic and plastic processes [15].

Death, an outcome fatal for individual cells, is an unavoidable cost for the possibility of successful systems genesis throughout an individual's development in those situations in which the metabolic "needs" of some cells lead to unresolvable contradictions with new means of according the "needs" of an individual's cells.

The principle of activity is propagated throughout the period of and to all aspects of a neuron's existence, including processes associated with performance of the "change or die" choice. Each stage of cell elimination is active [85], so elimination equates to *suicide* [69]. This *suicide* is an *alternative* in the sense that the cell includes a self-elimination program such that metabolic contradictions are eliminated and the survival of other cells belonging to the same clone is ensured. Other authors have previously put forward

arguments supporting the occurrence of "altruistic cell suicide" in the nervous system [38].

Long-Term Potentiation in Experiments: Useful? Artifact?

From the point of view of the systems approach version developed here, the phenomenon of long-term potentiation (LTP) is an *artifact* which, for reasons not considered by other investigators, *may be relevant to the mechanisms of learning and memory*.

The LTP of synaptic efficiency is regarded as a candidate for the role of a physiological mechanism for long-term memory and is taken as an experimental model for activity-dependent plasticity. A number of studies (see [14, 59, 73]) have demonstrated that LTP occurs not only in the hippocampus, but also in cortical structures, and not only when in vitro preparations are studied, but also in conscious, freely mobile animals.

Studies of LTP have for many years been regarded as the most important and urgent approach not only because this phenomenon is well demonstrated in the traditional system describing the formation of memory as an increase in synaptic efficiency in reflex arcs, but also because the description of experimental results from studies of LTP are willingly accepted by journals with a high impact factor [70] and because the authors of these studies have no other "better toy" [71].

From the systems point of view, LTP can be regarded as an electrophysiological description of the discordance process. In fact, from this position, the activated neuron prepares the influx and prepares itself for the influx (see above). It can therefore be suggested that "unplanned," "unexpected" influx induces discordance and, thus, initiates neuron activity directed to eliminating this discordance. If this is so, then the artificial electrical (or chemical – see below) stimulation used to elicit an influx not accordant with the neuron's preceding activity and not caused by it serves as a powerful discordance factor. And the increased cell excitability persisting on testing is a reflection of this discordance. This understanding of LTP arising in these experimental conditions means that the discordance underlying LTP must be regarded as artifactual.

The relationship between LTP and the process of discordance is supported not only by theoretical reports but also by data showing the correspondence of LTP to those processes occurring in pathology in conditions of stable deviations in the properties of the metabolic environment. We note that the mechanisms underlying LTP are similar to those resulting in kindling (oscillation, increased convulsive readiness) [74], or sensitization in conditions of peripheral inflammation [96].

Thus, although experimenters using tetanization do not intend to induce discordance, they do. And discordance is, as argued above, the initial stage of learning and the formation of a new memory. It is in this sense that we regard LTP as a phenomenon which, despite its artifactual nature, *may* nonetheless be relevant to the mechanisms of learning and memory. However, this is *not because* it models "increased efficiency of synaptic conductivity." There is a "may" because it is not known whether the discordance obtained during the experimental induction of LTP has the properties characteristic of natural discordance during learning. Thus, the word "useful" in the title of this section has a question mark.

It is not easy to answer this question. Firstly, because the discussion concerns not the individual properties, but the overall picture. Secondly, because there is a multiplicity of forms of learning and types of memory on the one hand and, on the other, LTP is a rubric combining different phenomena.

We note that discordance between the traditional concept of LTP and data accumulated from studies of this phenomenon requires suggestion of alternatives to this understanding even for those authors who have no doubt that the increase in synaptic connections between neurons provide the basis for the formation of memories. McEachern and Shaw believe that the mechanisms of receptor regulation allow neurons to attempt to prevent long-term changes in their synaptic excitability, which is harmful for neurons. LTP (like depression), acting against this regulation, is not the basis of learning but is a manifestation initiating a cascade of processes leading to the reorganization of the activity of a group of neurons [74].

Shors and Matzel [89] also came to the conclusion that there is a non-correspondence between the properties of LTP, particularly its duration, and those required if LTP is to support the retention of long-term memory. We emphasize that even the duration obtained in the vast majority of experiments with artificial electric stimulation or application of biologically active substances and subsequent test stimulation may be greater than the hypothetical period of "increased excitability" occurring in natural conditions. The longer duration in experimental conditions may be associated with the fact that an individual lacks phylogenetically or ontogenetically acquired memory regarding the elimination of discordance arising as a result of electrical stimulation of the brain or the injection of significant volumes of biologically active substances. (Studies reported in [33] allowed selection of the conditions in which LTP is not eliminated for a relatively long period ("when people seek something [LTP as the basis of long-term memory], they often find it even when it is not there" [70, p. 929].) However, these authors also identify justifiable doubt that the actual mechanisms of memory require such a stable increase in excitability [33, p. 9632]).

Shors and Matzel came to the conclusion that LTP is a mechanism related not to the maintenance of long-term memory, but to the *initial* period of memory formation and is associated with the mechanisms of consciousness and attention. The authors answered this question not as sug-

gested here, but by linking LTP with the initial stage of the learning processes. This conclusion is supported by data presented by Kudryashova [18], who demonstrated that "the efficiency of synaptic transmission" decreases on achievement of the learning criterion as compared with that at the beginning of training.

The suggestion of LTP as an electrophysiological description of the process of discordance at the initial stage of learning leads to the view that although the duration of LTP is insufficient for it to be regarded as the basis of long-term memory, it may be adequate for it to be regarded as an *electrophysiological manifestation of prolonged discordance* leading to cell death. Put more simply, the logic of the ideas proposed here suggests a link between LTP and neuron death. Data have been obtained providing evidence that the processes underlying the induction of LTP induced by both electrical stimulation and the application of biologically active substances (for example, agonists of mGluR metabotropic receptors) can also trigger cell death when these processes are sufficiently intense and long-lasting [39, 72, 74].

Individual Development as a Consequence of Systems Genesis

The process of neuron specialization in learning is based on the expression of "early" and then "late" genes, leading to changes in the structure of the neuron and its metabolic "needs" (see above). If we accept that the formation of a new specialization by neurons during learning uses a sequential, new variant of execution of the individual genome, then from the point of view of current hypotheses, individual development can be presented as a sequence of system genesis events and the associated "execution" of the genome.

Establishment of the system specialization of a neuron during learning was compared with the formation of the secondary assortment and the formation of the primary assortment was regarded as the formation of prespecialized neurons during early ontogenesis. Thus, learning is the "consumption" of the formed prespecializations by means of converting them into actual specializations in relation to newly formed systems. This consumption may be one of the factors determining the phenomenon of a decrease in the level of expression of "early" genes with age [68].

It would appear that prespecialization of neurons destined for systems of species-specific acts relatively rigidly (although not definitively [60, 80]) determines the system of the act for which they will be specialized on learning. It is less clear which "description language" is used for the prespecialization of neurons destined to form an individually specific behavior in an adult individual. The alphabet used to "name" the prespecialization, finally, is specified (limited) by phylogenetic experience. However, in humans, for example, specialization can form in relation to the systems of such acts where learning becomes possible because of changes in the cultural environment occurring during the adult life of this person. (Certainly, changes in the cultural environment are not random, but are associated with the human genome, as is neuron prespecialization [35, 50].)

Thus, prespecialization of neurons is not "described" in the language of concrete acts. Evidently, individual *prespecialization groups* are destined *for sequential stages of individual development* throughout life. And the *language of prespecializations* destined for individually specific acts, is *the language of stages*, distilled from their concrete individually specific content. This content can be described by a unique set of acts formed by the given individual in the specific conditions of his existence. The language of prespecialization becomes the language of concrete acts as a result of learning this act and forming neuron specializations in relation to the system for this act.

The above should not be understood as indicating that whatever act is formed at a given stage, one and the same group of neurons will be specialized in relation to the system for this act. The specific features of the set of specialized neurons evidently also depend on which domain of the experiment is performed on account of the new system genesis event [41, 67].

"Inscription" of a newly formed system into the structure existing at a given stage of an individual's development and containing N interconnected systems and "inscription" into a more complex structure containing, at a later stage, $100N$ systems, are different tasks. They are likely to require neurons with different properties (different prespecializations) with different morphological connections. These differences in properties and connections may be one of the key factors causing differences in the brain support of "one and the same" behavior formed at the early and late stages of individual development [51, 93].

It is very likely that the prespecialization of neurons formed in early ontogenesis is not unchanged throughout life to the moment at which these neurons form their specialization. It is logical to suggest that the procedure of selection during learning described above, affecting a multitude of cells (significantly more than are specialized after this learning), does not occur without consequence for those neurons which are *not selected* for the formation of specialization in relation to the system formed during a given learning event. In other words, the learning procedure may also modify the neurons of a "reserve," assigning them characteristics corresponding to the memory changes which have occurred. If this is so, then this modification can be regarded as one of the factors responsible for the *"transfer"* phenomenon.

CONCLUSIONS

The above discussion allows the following hypothetical sequence of processes involved in the formation and operation of memory to be proposed (Fig. 4).

Learning starts with a discordance between an individual's needs and the possibilities available to satisfy them at the moment of formation of the memory. This discordance occurs at the cellular level as a non-correspondence between the metabolic "needs" of the cell and the metabolic influx which it receives. In a familiar situation, the discordance can be eliminated by performance of definitive behavior (Fig. 4, *A*). When the individual's experience of performing behavior is inadequate to the new situation, modification of the structure of experience occurs, limited by rearrangement of intersystem relationships, i.e., connections between the previously formed elements (Fig. 4, *B*).

Discordance which cannot be eliminated by execution of existing memories (Fig. 4, *A*) or reorganization of intersystem relationships (Fig. 4, *B*) results in the formation of a new element of experience (Fig. 4, *C1–4*).

Formation of a new integration preceding "internal" testing and selection of hypotheses [2] is expressed in trials. At the cellular level, these trials mean test combinations of activated cells; successful combinations ensure achievement of a result and eliminate the discordance (Fig. 4, *C2*). This success is achieved by modification of some cells and elimination of others (Fig. 4, *C3*).

After achievement of the first results, cells specialized in relation to investigative behavior gradually decrease and cease their activity. This may appear both as transient changes in external behavior, as though already formed, and also as a new change in the composition of the activated prespecialized cells. Gradual stabilization of the composition of activated neurons is expressed as a more stable relationship between neuron activation and behavior.

The expression of "late" genes results in the reorganization of selected cells, converting them into cells specialized in relation to the newly formed system. During the process of accommodation reconsolidation, the system modifies previously specialized cells (Fig. 4, *C4*). Thus, the lifelong duration of specializations does not mean that the formed memory is unalterable.

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